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RESEARCH ARTICLE

INITIAL MANAGEMENT OF FROZEN ADDICT: AN UPDATE

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ABSTRACT

Frozen Addicts are one of the leading causes of death. The World Health Organization (WHO) lists 126 central nervous system disorders. Although the cause of frozen addict are unknown, each year approximately 1,90,000 people in the United States and 10,000 people in Canada will be diagnosed with a primary symptoms. Frozen addicts are the number two cause of disability in men age 40 and older. Only 31 percent of males and 30 percent of females survive/recover five to fifteen years following the diagnosis of primary symptoms. Enhancing the quality of life of people with frozen addict requires access to quality specialty care, clinical trials, follow-up care and rehabilitative services. Although genes that are linked to monogenic forms of Parkin's disease a and other closely related neurodegenerative diseases are, at first glance, not related to a coo man cause , recent genetic, pathologic and molecular studies have strengthened the evidence that there is probably more "cross talk" between the different pathway, on several levels, then previously appreciated. These finding support the existence of common pathogenic mechanisms, protein aggregiation, mitochondrial dysfunction or oxidative stress, which had been suspected as major culprits of neurode generation for many years. This review tries to demonstrate that during routine office visits, neurologist failed to identify the presence of depression, anxiety, and fatigue more than half of the time failed to recognize sleep disturbance in 40% of patients. Awareness of likelihood under recognition of behavioral symptoms in PD should generate approaches to diagnostic accuracy and facilitate timely therapeutic interventions.

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INTRODUCTION

A California neurologist, in 1982, began investigating a bizarre disease outbreak: patients with bent and twisted bodies, faces stiffened to the point that some were drooling uncontrollably, even in the summer heat resembling bodies frozen to rigidity. In 1982, a student in California synthesized a new and very dangerous form of heroin called MPTP. This form of the drug selectively attacks the nerve cells in the brain that are lost in Parkinson's. Anyone who took heroin contaminated with the MPTP developed very severe Parkinson's-like symptoms almost immediately. These unlucky people became known as the 'Frozen Addicts', but their misfortune has led to significant scientific advances. MPTP has since been widely used in research and helped scientists learn much more about how and why nerve cells die in the condition. (Langston, 2002)

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Historical background

Frozen shoulder syndrome (FSS) is a commonly recognized clinical complaint. It is encountered by clinicians (General Practitioners, rheumatologists, orthopedic surgeons) and physical therapists (physiotherapy, osteopathy, chiropractic). Defining 'frozen shoulder' is not straightforward. It has been used incorrectly as a general diagnosis for shoulder pain and stiffness. The definition, aetiology, path physiology and treatment of this condition are subjects of debate. Since first being described by Duplay in 1872 various attempts have been made to define and categorize frozen shoulder. I shall define frozen shoulder syndrome after Grubbs as 'a soft tissue capsular lesion accompanied by painful and restricted active and passive motion at the glen humeral joint. Frozen shoulder affects females slightly more than males typically between 40 and 60 years of age. The non-dominant arm is more likely to be involved, although about 12% of people are affected bilaterally. Frozen shoulder syndrome is common affecting 2-5%of the general population, whilst in diabetics the incidence

is between 10-20%. Other factors such as depression, immunologic factors, posture and occupation have been implicated in the etiology. The natural history of this condition is well documented. Frozen shoulder passes through the three phases of freezing, frozen and thawing. The average duration of symptoms is 30 months. The freezing (painful) phase lasts between two and a half and eight months. Night pain is a common feature of this phase. This is followed by the frozen (stiff) phase, which lasts between four and 12 months. There still may be night pain but this usually diminishes as gleno humeral mobility decreases. Spontaneous recovery of mobility Simeon Neil-Asher Frozen Shoulder Syndrome Simeon Neil-Asher has commenced a randomized controlled clinical trial in the Cambridge area. The research is a randomized placebo controlled trial involving three treatment modalities: Osteopathy physiotherapy placebo. All patients have an initial consultation with a senior research physiotherapist who assesses them with various quantitative and qualitative tests (one and a half hours). Patients are then randomized to one of the three treatment options, six 45 minute treatments are performed on Thursdays over nine weeks and patients are evaluated after the third and sixth treatment. When the trial is complete the results should be published in the British Journal of Rheumatology. More patients need to be recruited for the trial. Treatments take place on Thursdays in the Cambridge area. (Reeves, 1975)

Etiology

Viral infections: There is some evidence that viral infections may increase a person's risk of developing Parkinson's. In the 1920s there was an epidemic of encephalitis ('sleeping sickness') that may have been a viral infection. Many of the survivors went on to develop Parkinson's-like symptoms. Researchers think this may be due to inflammation in the brain. Inflammation is now a hot topic in Parkinson's research and we're funding several projects to see how inflammation may be involved and whether reducing inflammation in the brain could be a fruitful avenue for developing new treatments.

Exposure to chemicals: Some evidence also links exposure to certain types of chemicals to an increased risk of developing Parkinson's.

A study of men who'd been exposed to the chemical solvent TCE regularly in their work found they were more than six times more likely to develop Parkinson's compared to their twins without such exposures. But this was a small study and still needs to be confirmed in larger population. (De Lau and Breteler, 2006)

Clinical Forum: 22 December (thawing) follow over the next four to 12 months although full recovery is commonly protracted. After the thawing phase an objective restriction of mobility may often persist for several years. The most commonly affected movements are external rotation and abduction of the glen humeral joint. Patients commonly complain of sharp pain reaching for the back pocket, combing the hair, or doing up their bra. The arm does not swing when walking. At rest the arm is often held in adduction and internal rotation, and the scapula of the affected side is usually elevated, laterally rotated and abducted. Depending on the longevity of symptoms, the body may develop a compensatory mechanical adaptation Current treatment. There is no unanimous opinion regarding the proper method of treatment. A great number of therapeutic regimes have been advocated, but none have proved consistently successful. The first line of treatment is usually a course of oral analgesic drugs such as NSAIDs, with physical therapy. It is believed that physical therapy is of little or no use during the freezing or frozen phases, but may help speed up recovery during the thawing phase. The GP may initiate a course of hydrocortisone injections into the shoulder; these are rarely useful on their own. Patients may have more than a dozen physical therapy sessions during this time including ultrasound, mobilization and exercise regimens. Transcutaneous Electrical Nerve Stimulation (TENS) machines are also commonly used to alleviate night pain. The next stage is often referral for one of several more invasive treatment options. This includes manipulation under an aesthesia (MUA) followed by several months of intensive physical therapy, or if severe, more invasive surgery. The risks associated with MUA include fracture of the humorous, tendon rupture and brachial plexus injury. As recently as 1997 several clinical trials have shown that none of the above treatments gives consistently reproducible success. Osteopathy and Frozen Shoulder Osteopathic texts fail to illuminate the 'osteopathic pathology' and/or a treatment regimen for FSS. 'No generally accepted guidelines for the treatment exist.

Several texts offer a vague outline for treatment. They advise soft tissue treatment of the shoulder muscles combined with basic home exercise programmes and the 'correction' of 'lesions' in the thoracic spine, sternoclavicular and acromioclavicular joints. American texts go on to promote the use of local steroid injections or prophylactic Prednisolone in the early phase of the syndrome concluding 'the injection may give only temporary relief and may have to be repeated at regular intervals. Other texts seem to regurgitate and paraphrase orthopaedic books talking about treatment in the vaguest of terms. They are mainly descriptive, the preeminent advice being 'prevention is the best treatment. Older texts fail to mention FSS as an entity; they see it as the sequelae in breakdown of proper and free joint movements. Indeed AT Still felt that a large percentage of painful shoulders had the distal end of the clavicle pushed too far back. Texts on strain and counter strain offer only a few techniques and these are mainly for 'home managed pain relief. A survey of acupuncturists, chiropractors, doctors, osteopaths and physiotherapists attitudes to FSS12 was carried out in 1996. The conclusions were that there seems to be a great deal of ignorance about FSS. Osteopaths mainly view FSS as having a multi-factorial aetiology, requiring between 11-15 sessions of treatment for maximum benefit (preferably in the frozen phase). Osteopaths, chiropractors and physiotherapists had a similar approach to treatment.

Symptoms

- Unilateral shoulder pain and stiffness
- Age 40-70
- 6 months plus symptom duration

- No underlying articular or soft tissue pathology
- No previous shoulder surgery.

Simeon Niel-Asher scanning a patient with the Toshiba ECCOCEE Ultrasound machine which was lent to him for the study.

The osteopathic approach was based on the following four elements

- Stretching tight soft tissue structures
- Neuromuscular technique
- Articulation into the painful range (increasing Range Of Motion)
- Exercises for rehabilitation of wasted muscles Discussions with colleagues has yielded additional treatment approaches including:
- Addressing any associated 'osteopathic lesions'
- Treating the opposite side of the cervical spine
- Working on the postural compensations for FSS using muscle energy, active resisted and functional techniques
- Visceral techniques to the ligamentous structures of the abdominal viscera with their direct and indirect attachments to the diaphragm and shoulder girdle some practitioners claim success using cranio-sacral therapy.

Others hold that the shoulder tissues are manifesting emotional blockages often asking the patient 'what is frozen in your life.' Most authorities agree that a regime of physical therapy is beneficial for FSS. Unfortunately there is little or no unanimity in the diagnostic or therapeutic approaches to this painful and debilitating condition. From an extensive literature search neither medical orthodoxy nor osteopathy offer either of the above. 23 December '00/January '01 FSS could provide an excellent vehicle for extolling the virtues of a 'drug-free' osteopathic approach to treatment. It affords a homogenous research population. It has a well-documented natural history (unlike the notoriously 'labile' low back) and lends itself to both qualitative and quantitative research. (Grubbs, 1993)

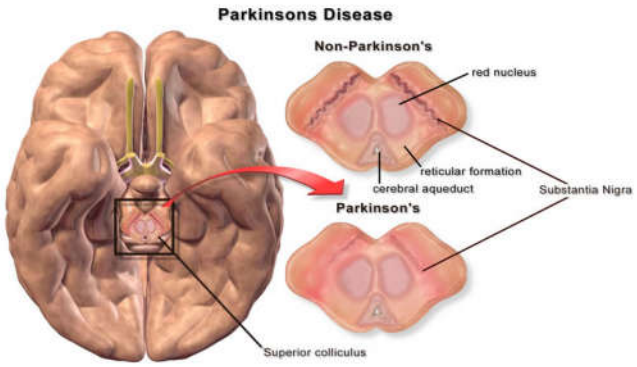

Fig. Human Brain parts effected by Parkinson 's disease (Mortiboys *et al*., 2015)

Idiopathic Parkinson's disease (Pd): It is a progressive neurological condition which is characterized by motor (movement) and non-motor symptoms. Idiopathic Pd is characterized pathologically by the loss of dopamine producing neurons in the substantial nigra within the mid-brain. While this is not the only pathological feature of the condition it is evident in all cases at post mortem. Another major feature is the presence of Lewy bodies. These are concentric inclusion bodies which can be identified by using red dye called eosin. (Foundations for Osteopathic Medicine: 560: American Osteopathic Association: Williams and Wilkins 1995)

Symptoms of Parkinson disease: Rhythmic tremor often occurs at first in one hand, where it resembles the motion of rolling a pill between the thumb and forefinger. Muscle rigidity shows itself in the cogwheel phenomenon: pushing on an arm causes it to move in jerky increments instead of smoothly. Leaning forward or backward when upright reflects impairment of balance and coordination.

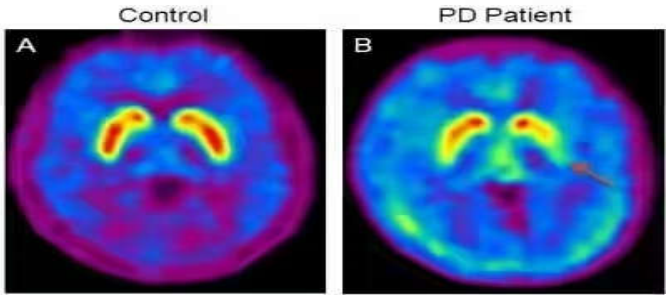

Fig. 2. Neurographic Image of Control &PD effected patient (Micheli and Cersosimo, 2007)

Difficulty rising from a sitting position is a common sign of disordered control over movement. Some patients report feelings of weakness and of being restrained by ropes or other external forces. Shrinkage of handwriting is a symptom in some people. The samples show writing when patient's medicine was working (top) and when it was not (bottom). (Mortiboys *et al*., 2015)

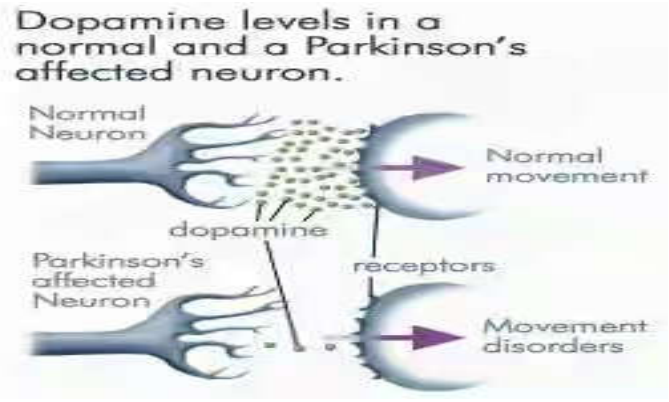

Fig. 3. Dopamine levels in a normal and a Parkinson's affected neuron. (Olanow *et al*., 1996)

Drug causing frozen and Parkinson's syndrome : MPTP: (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a neurotoxin precursor to MPP+, which causes permanent symptoms of Parkinson's disease by destroying dopaminergic neurons in the substantia nigra of the brain. It has been used to study disease models in various animal studies. While MPTP itself has no psychoactive effects, the compound may be accidentally produced during the manufacture of MPPP, a synthetic opioid

drug with effects similar to those of morphine and pethidine (meperidine). (Langston, 2002)

Mechanism of MPTP: Induced Toxicosis after systemic administration, MPTP crosses the blood-brain barrier. It is converted to 1-methyl-4-phenyl-2,3- dihydropyridinium (MPDP+) by monoamine oxidase B (MAO-B, principally in astrocytes), then spontaneously oxidizes to 1-me- thyl-4-pyridinium (MPP+), its toxic form. The MPP+ acts as a substrate of the dopamine transporter (DAT) and is taken up by SNpc neurons, leading to inhibition of mitochondrial complex I, depletion of ATP, generation of reactive oxygen species, and death of dopaminergic neurons. Administration of MPTP to mice and nonhuman primates destroys dopaminergic neurons of the SNpc, the same neurons affected in patients with PD R[1.] Similar to PD, other catecholaminergic neurons, such as those in the ventral tegmental area (VTA) and locus coeruleus, are affected, but to a lesser degree. In addition, dopamine is depleted in the put amen and caudate nucleus, targets of the SNpc neurons. The preferential lesioning of either the put amen or caudate nucleus may depend on animal species and regimen of MPTP administration. Unlike PD, Lewy bodies have not been reported in MPTP-lesioned animals; however, eosinophilic inclusions (reminiscent of Lewy bodies) have been described in aged non- human primates.

The time course of MPTP-induced neuro degeneration is rapid and, therefore, represents a major divergence from the chronic progressive disease course typical of idiopathic PD. Interestingly, data from humans exposed to MPTP indicate that the toxic effects of MPTP may be more protracted than was initially believed R[2.] Numerous factors, including species, strain, and age of the animal, contribute to the sensitivity to and toxic effects of MPTP. For example, the nonhuman primate is very sensitive to the toxic effects of MPTP. In particular, Old World monkeys are more sensitive than are New World monkeys. The mouse, cat, dog, and guinea pig are less sensitive, and the rat is the least sensitive. There are strain differences within species transgenic genes. They include bioavailability of MPTP and MPP+ through interactions with peripheral organs, especially detoxification enzymes found in the liver; ability of MPTP to cross the blood-brain barrier (especially conversion to MPP+ (which cannot cross) in the periphery); uptake of MPP+ via the dopamine transporter; storage and sequestering of MPP+ in vesicles; and interaction of MPP+ with mitochondrial enzymes. Age is another factor that influences the sensitivity of animals to the neurotoxicity effects of MPTP; older mice (and nonhuman primates), for example, are more sensitive to MPTP-lessoning metabolism. (Abeliovich *et al*., 2000)

Toxicity

Injection of MPTP causes rapid onset of Parkinsonism, hence users of MPPP contaminated with MPTP will develop these symptoms. MPTP itself is not toxic, and as a lipophilic compound can cross the blood–brain barrier. Once inside the brain, MPTP is metabolized into the toxic cation 1-methyl-4-phenylpyridinium (MPP+) by the enzyme MAO-B of glial cells. MPP+ kills primarily dopamine-producing neurons in a part of the brain called the pars compact of the substantia nigra. MPP+ interferes with complex I of the electron transport chain, a component of mitochondrial metabolism, which leads to cell death and causes the buildup of free radicals, toxic molecules that contribute further to cell destruction. Because MPTP itself is not directly harmful, toxic effects of acute MPTP poisoning can be mitigated by the administration of monoamine oxidase inhibitors (MAOIs) such as selegiline. MAOIs prevent the metabolism of MPTP to MPP+ by inhibiting the action of MAO-B, minimizing toxicity and preventing neural death.MPP+ has quite selective abilities to cause neuronal death in dopaminergic cells, it is presumed through a high-affinity uptake process in nerve terminals normally used to reuptake dopamine after it has been released into the synaptic cleft. The dopamine transporter moves MPP+ inside the cell. The resulting gross depletion of dopaminergic neurons has severe implications on cortical control of complex movements. The direction of complex movement is based from the substantia nigra to the put amen and caudate nucleus, which then relay signals to the rest of the brain. This pathway is controlled via dopamine-using neurons, which MPTP selectively destroys, resulting over time in parkinsonism. MPTP causes Parkinsonism in primates including humans. Rodents are much less susceptible. Rats are almost immune to the adverse effects of MPTP. Mice were thought to only suffer from cell death in the substantia nigra (to differing degree according to the strain of mice used) but do not show Parkinson an symptoms, however most of the recent studies indicate that MPTP can result in Parkinsonism-like syndromes in mice (especially chronic syndromes).

Synthesis: MPTP was first synthesized as an analgesic in 1947 by Ziering *et al*. by reaction of phenyl magnesium bromide with 1-methyl-4-piperidinone. It was tested as a treatment for various conditions, but the tests were halted when Parkinson-like symptoms were noticed in monkeys. In one test of the substance, two of six human subjects died. (Langston, 2002)

Administration of MPTP

A. Animals must be chemically or physically restrained prior to starting the procedure.
B. Administration of MPTP to rodents must be conducted in a certified chemical fume hood or at a certified down draft table. Both the personnel administering the MPTP and those in the immediate vicinity of the procedure must wear appropriate PPE.
C. All work surfaces, except the down-draft table, must be covered with absorbent, plastic-backed, disposable bench paper.
D. Use only needle-locking syringes or disposable syringe-needle units (i.e., needle is integral to the syringe). Used disposable needles must not be bent, sheared, broken, recapped, removed from disposable syringes, or otherwise manipulated before disposal. After the completion of each injection, immediately place the syringe-needle unit in a sharps disposal container. The sharps disposal container shall be disposed of in an MPW box at the end of each day.

Advantages of MPTP: MPTP model: Mouse>

- Inexpensive, small, easy to handle
- Genetically identical strains

- Animal of different ages and sensitivity available

Mild acute lesion

- High degree of animal survival
- Mild cell loss
- Mild dopamine depletion

Chronic Lesions

- High survival
- Progressive cell death

Nonhuman Primates

- Neuroanatomy resembles human
- Motor behavioral features similar to human

Disadvantages: Mouse

- Neuroanatomical difference compared with primates
- Motor behavioral features different from primates
- Variability in stain susceptibility. (Langston, 2002)

Mild acute lesions

- Variability in degree of lessoning
- Lesions may be too mild foe some studies Robust recovery

Chronis Lesions

- Requires consistent lessoning administration for reproducibility
- Long lessoning period

Nonhuman Primates

- Expensive
- Experiments have small number
- Out bred with variability in motor behavior deficits

Drugs for a treatment

Pramipexole: Pramipexole has been well studied as monotherapy in patients with early-stage PD, and as an adjunct to levodopa therapy in advanced stage disease. These trials were multicenter, placebo-controlled, parallel-group studies, and the primary out-come measures included improvement in ADLs (part II) and motor function scores (part III) as measured by the Uni ed Parkinson Disease Rating Scale (UPDRS). Each evaluation on the UPDRS is rated on a scale of 0 (normal) to 4 (canbarely perform). Lower scores on the UPDRS after treatment indicate an improvement in overall performance. The evidence for (mg/day) and then followed patients for a 6-month maintenance phase. The mean pramipexole maintenance dosage was 3.8mg/day. Those treated with pramipexole experienced signi cant improvements in both the ADL scores (22%–29%) and motor scores (25%–31%), whereas there were no signi cant changes in the placebo group ($p < 0.0001$). Against levodopa as initial therapy, pramipexole appears to delay the onset of dyskinesias. In a randomized, controlled trial evaluating the development of motor complications with the two therapies, 301 untreated patients with early PD were randomly assigned to receive either pramipexole 0.5mg three times daily or carbidopa/levodopa 25/100 mg three times daily.23 Doses could be escalated during the rst 10 weeks of the study, after which open-label levodopa was permitted if necessary. The primary end point was the time to the rst occurrence of wearing off, dyskinesias, or on-off motor uctuations. After a mean follow-up of 24 months, patients in the pramipexole group were receiving a mean daily dose of 2.78 mg pramipexole and 264 mg of sup-plemental levodopa, whereas patients in the levodopa group were receiving a mean total of 509 mg/day levodopa. Fewer pramipexole treated patients reached the primary end point (28% vs. 51%; $p < 0.001$) than the patients initially randomly assigned to levodopa therapy. Dyskinesias were noted in only 10% of pramipexole-treated patients compared with 31% of levodopa-treated patients ($p < 0.001$), and fewer patients experienced wearing-off effects with pramipexole (24% vs. 38%; p= 0.01). Long-term follow-up of this cohort (mean=6.0years) has revealed a persistently lower rate of dopaminergic motor complications in the pramipexole treated patients compared with those receiving levodopa (50.0%vs.68.4%, respectively; p=0.002). (Fritz *et al*., 1985)

Ropinirole: Ropinirole is a synthetic nonergoline dopamine agonist with selectivity for D2 receptors; as with pramipexole, however, it has no signi cant affinity for D1 receptors. Although the drug is pharmacologically similar to pramipexole, it has some distinct pharmacy kinetic properties. Unlike pramipexole, which is primarily eliminated by renal excretion, ropinirole is metabolized by the cytochrome P-450 (primarily CYP1A2) oxidative pathway and undergoes signi cant rst-pass hepatic metabolism. Similar to pramipexole, ropinirole approved for use as monotherapy in early-stage idiopathic PD and adjunct to levodopa therapy in patients with advanced-stage disease. Ropinirole has not been directly compared with pramipexole in a randomized, double-blind trial, but it appears to have comparable efficacy as inferred from indirect comparison. In several randomized, double-blind, multicenter, parallel group studies comparing it with placebo, bromocriptine, or levodopa, 6 months of monotherapy with ropinirole in patients with early PD signi cantly improves UPDRS motor scores (approximately 20%–30%) compared with baseline values. In a long-term study, patients treated initially with ropinirole were less likely to experience dyskinesias compared with those treated initially with levodopa. At the end of 5 years, the mean daily dose of ropinirole was 16.5 mg plus 427 mg of open-label levodopa, compared with a mean daily dose of 753 mg of levodopa for the levodopa group. Of patients in the ropinirole group, 66% required open-label levodopa supplementation compared with 36% in the levodopa group. Dyskinesias developed in 20% of the ropinirole-treated patients compared with 45% of the levodopa- treated patients (hazard ratio for remaining free of dyskinesia in the ropinirole group, compared with the levodopa group, 2.82; $p < 0.001$). For ropinirole-treated patients who were able to remain on monotherapy without open-label levodopa supple- mutation, only 5% experienced dyskinesia, compared with 36% of those receiving levodopa monotherapy.

The lower incidence of dyskinesia in ropinirole-treated patients was shown to persist in long-term open-label follow-up of this study cohort. (Nutt and Wooten, 2005)

Adverse effects: Because pramipexole and ropinirole are both approved for use as monotherapy in early-stage disease and as adjunctive therapy in advanced-stage disease. The adverse events of these agents have been evaluated as a function of disease stage. In studies of patients with early-stage disease, the most common adverse effects were nausea dizziness, somnolence, insomnia (~17%), constipation (~14%), asthenia (~14%), hallucinations (~9%), and leg edema (~5%).Nausea, with or without vomiting, can be a signi cant problem, particularly with higher doses. Administering these drugs with food may partially all eviatet his problem. With continued use, many patients exhibit tolerance to the gastrointestinal side effects. Central nervous system side effects were the most common reason for discontinuation of these agents. Older patients are particularly more likely to experience hallucinations and other central nervous system adverse effects with dopamine agonists. The incidence of orthostatic hypotension was relatively low (1%–9%) and may impart re ect the exclusion of patients with underlying cardiovascular disease in several of the studies. (Morley and Hurtig, 2010)

Selegiline

Selegiline hydrochloride is a levorotatory acetylenic derivative of phenethylamine. It is commonly referred to in the clinical and pharmacological literature as l- deprenyl. The chemical name is: (R)-(-)-*N*, α-Dimethyl-*N*-*2*-propynylphenethylamine hydrochloride. It is a white to near white crystalline powder, freely soluble in water, chloroform, and methanol, and has a molecular weight of 223.75. The molecular formula is C13H17N.HCI. Each capsule, for oral administration contains 5 mg of Selegiline hydrochloride. In addition, each capsule contains the following inactive ingredients: Anhydrous Lactose NF, Citric Acid Anhydrous USP, Microcrystalline Cellulose NF PH102, Stearic Acid NF and Talc USP. The capsule shell contains Gelatin NF, FD & C Blue #1 and Titanium Dioxide. The capsule logo ink Black SW-9008/SW-9009 contains the following inactive ingredients: Ammonium Hydroxide; Black Iron Oxide, Bacteria Controlled EEC No. 172; n-Butyl NF; Ethyl Alcohol, Anhydrous, 200 Proof; Isopropyl Alcohol USP; Potassium Hydroxide NF; Propylene Glycol USP; Purified Water USP and Shellac NF.

Selegiline - Clinical Pharmacology

The mechanisms accounting for Selegiline's beneficial adjunctive action in the treatment of Parkinson's disease are not fully understood. Inhibition of monoamine oxidase, type B, activity is generally considered to be of primary importance; in addition, there is evidence that Selegiline may act through other mechanisms to increase dopaminergic activity. Selegiline is best known as an irreversible inhibitor of monoamine oxidase (MAO), an intracellular enzyme associated with the outer membrane of mitochondria. Selegiline inhibits MAO by acting as a 'suicide' substrate for the enzyme; that is, it is converted by MAO to an active moiety which combines irreversibly with the active site and/or the enzyme's essential FAD cofactor. Because Selegiline has greater affinity for type B rather than for type A active sites, it can serve as a selective inhibitor of MAO type B if it is administered at the recommended dose. MAOs are widely distributed throughout the body; their concentration is especially high in liver, kidney, stomach, intestinal wall, and brain. MAOs are currently sub classified into two types, A and B, which differ in their substrate specificity and tissue distribution. In humans, intestinal MAO is predominantly type A, while most of that in brain is type B. In CNS neurons, MAO plays an important role in the catabolism of catecholamine's (dopamine, nor epinephrine and epinephrine) and serotonin. MAOs are also important in the catabolism of various exogenous amines found in a variety of foods and drugs. MAO in the GI tract and liver (primarily type A), for example, is thought to provide vital protection from exogenous amines (e.g., tyramine) that have the capacity, if absorbed intact, to cause a 'hypertensive crisis,' the so-called 'cheese reaction.' (If large amounts of certain exogenous amines gain access to the systemic circulation e.g., from fermented cheese, red wine, herring, over-the-counter cough/cold medications, etc. they are taken up by adrenergic neurons and displace nor epinephrine from storage sites within membrane bound vesicles. Neither subsequent release of the displaced nor epinephrine causes the rise in systemic blood pressure, etc.) In theory, since MAO A of the gut is not inhibited, patients treated with Selegiline at a dose of 10 mg a day should be able to take medications containing pharmacologically active amines and consume tyramine-containing foods without risk of uncontrolled hypertension. Although rare, a few reports of hypertensive reactions have occurred in patients receiving Selegiline at the recommended dose, with tyramine-containing foods. In addition, one case of hypertensive crisis has been reported in a patient taking the recommended dose of Selegiline and a sympathomimetic medication, ephedrine. The path physiology of the 'cheese reaction' is complicated and, in addition to its ability to inhibit MAO B selectively, Selegiline's relative freedom from this reaction has been attributed to an ability to prevent tyramine and neither other indirect acting sympathomimetics from displacing nor epinephrine from adrenergic neurons. However, until the path physiology of the 'cheese reaction' is more completely understood, it seems prudent to assume that Selegiline can ordinarily only be used safely without dietary restrictions at doses where it presumably selectively inhibits MAO B (e.g., 10 mg/day). (Miyasaki J Metal, 2006)

Levodopa: Dopamine itself does not cross the blood–brain barrier. Levodopa, a dopamine precursor with no known pharmacologic action of its own, crosses the blood–brain barrier, where it is converted by aromatic amino acid (dopa) decarboxylase to dopamine. For patients with advancing PD, levodopa has been a mainstay of treatment since the 1960s. nearly all patients will eventually require treatment with the drug, regardless of the initial therapy. Although it is the most effective therapy for treating the rigidity and Brady kinesis of PD, as with other dopaminergic agents, levodopa does not effectively improve postural instability, or reduce dementia, autonomic dysfunction, or freezing, an extreme type of a kinesis that often occurs in advanced-stage disease. The question of when to begin levodopa in the treatment of PD has been historically debated. With long-term use, the efficacy of levodopa decreases (as measured by the total on time), and the development of motor uctuations and dyskinesias occurs.

Marketed formulations available for Parkinson's disease

S.No.	Class	Example Of drugs	Manufacturing Company	Use	Adverse Effects
1.	Dopaminergic agonist	Pramipexole	Cipla	Parkinson's Disease (PD)	Nausea, dizziness, Hallucination, postural Hypotension
2.	Dopaminergic precursor	Levodopa	Taj Pharmaceuticals	PD	Nausea, vomiting, Postural hypotension, cardiac Arrhythmias, behavioural Effects
3.	MAO-B Inhibitors	Selegline, Rasagiline	Taj Pharmaceutical	PD	Postural hypotension, Nausea Confusion, psychosis.
4.	Dopaminergic agonist	Bromocriptine	Taj Pharmaceuticals	Hyper-prolactinemia, PD	Nasal-stuffiness, hypotension, Hallucination, vomitting
5.	Dopaminergic agonist	Ropinirole	Dr.Reddys Labortatory and Sun Pharmaceuticals	PD, Restless leg Syndrome	Nausea, dizziness, Hallucination, postural Hypotension

These observations led to the belief that chronic levodopa therapy may actually accelerate the neurodegenerative process through formation of free radicals generated by dopamine metabolism. The Earlier versus Later Levodopa Therapy in Parkinson's Disease (ELLDOPA) study was designed to determine whether long-term use of levodopa accelerates neurode- generation and paradoxically worsens PD. The investigators of this study randomly assigned 361 patients with early PD to either carbidopa/levodopa37.5/150mg/day, 75/300mg/day, or 150/600 mg/day or placebo for 40 weeks followed by a 2-week withdrawal of treatment. After 42 weeks, the severity of symptoms as measured by changes in the total UPDRS increased more in the place group thaninal of the groups receiving levodopa. The ndings of this study provide assurance that levodopa use does not result in accelerated progression of the disease based on clinical evaluations. The optimal time to initiate levodopa therapy must be individualized .In untreated individuals, there is little reason to start levodopa until the patient reports worsening of function (socially, vocationally, or otherwise). Although the dose of pramipexole could be increased, he may experience more daytime somnolence; thus, levodopa should be added to his regimen.

Levodopa: Advantages and Disadvantages

Although levodopa is the most effective agent for PD, it is associated with many undesirable side effects, such as nausea, vomiting, and anorexia (50% of patients); postural hypotension (30% of patients); and cardiac arrhythmias (10% of patients). In addition, mental disturbances are encountered in15% of patients, and abnormal involuntary movements (dyskinesias) can be seen in up to 55% of patients during the rst 6 months of levodopa treatment. Because signi cant amounts of levodopa are peripherally (extra cerebrally) metabolized to dopamine by the enzyme aromatic amino acid (dopa) decarboxylase, extremely high doses are necessary if administered alone. For this reason, levodopa is always co administered with a dopa decarboxylase inhibitor. By combining levodopa with a dopa decarboxylase inhibitor that does not penetrate the blood–brain barrier, a decrease in the peripheral conversion of levodopa to dopamine can be achieved, while the desired conversion within the basal ganglia remains unaffected The two peripheral decarboxylase inhibitors in clinical use are benserazide (unavailable in the United States) and carbidopa. A xed combination of carbidopa and levodopa is available in ratios of 1:4 (carbidopa/levodopa 25/100) and 1:10 (carbidopa/levodopa 10/100 and 25/250). A controlled-release product is available in a ratio of 25/100 and 50/200. In addition, carbidopa/levodopa is also available as an orally disintegrating tablet. Combining carbidopa with levodopa enhances the amount of dopamine available to the brain and thereby allows the dose of levodopa to be decreased by 80%. This combination also shortens the time needed to achieve optimal effects by several weeks, because carbidopa substantially decreases the often dose- limiting levodopa-induced nausea and vomiting. Although more commonly encountered with dopamine agonists, psychiatric side effects are also associated with levodopa therapy, and include confusion, depression, restlessness and over- activity, psychosis, hypomania, and vivid dreams. Those with underlying or preexisting psychiatric disorder and those receiving high dose of levodopa for prolong period sareat greatest risk. Concurrent anticholinergics or amantadine therapy can exacerbate these symptoms. (Morley and Hurtig, 2010)

Objective of the study

The main objective of the present review work is given as follows:

- The main objective is to gain all the background information about the frozen addict, their etiology, symptoms, pathology, epidermology & feasible treatment for the same.
- To know the novel techniques and advancements available in the field of drug delivery system.
- To know the unwanted effects/ADR of the drugs used for treatment.
- To check the combination therapy of drugs (if any available) for the best possible results.

LITERATURE REVIEW

Zesiewicz *et al.* reported that, Non-motor symptoms (sleep dysfunction, sensory symptoms, autonomic dysfunction, mood disorders, and cognitive abnormalities) in Parkinson disease (PD) are a major cause of morbidity, yet are often under recognized. This evidence-based practice parameter evaluates treatment options for the non motor symptoms of PD. Articles pertaining to cognitive and mood dysfunction in PD, as

well as treatment of sialorrhea with botulinum toxin, were previously reviewed as part of American Academy of Neurology practice parameters and were not included here. Methods: A literature search of MEDLINE, EMBASE, and Science Citation Index was performed to identify clinical trials in patients with non-motor symptoms of PD published between1966 and August 2008. Articles were classified according to a 4 tiered level of evidence scheme and recommendations were based on the level of evidence. Results and Recommendations: Sildenafil citrate (50mg) may be considered to treat erectile dysfunction in patients with Parkinson disease (PD) (Level C). Macrogol (polyethylene glycol) may be considered to treat constipation in patients with PD (Level C). The use of levodopa/carbidopa probably decreases the frequency of spontaneous night time leg movements, and should be considered to treat periodic limb movements of sleep in patients with PD (Level B). There is insufficient evidence to support or refute specific treatments for urinary in continence, orthostatic hypotension, and anxiety (Level U). Future research should include concerted and interdisciplinary efforts toward finding treatments for nonmotor symptoms of PD. (Zesiewicz *et al.,* 2009)

Murat Emr *et al.* reported that Cholinergic deficits are prominent in patients who have dementia associated with Parkinson's disease. We investigated the effects of the dual cholinesterase inhibitor rivastigmine in such patients. Methods Patients in whom mild-to-moderate dementia developed at least 2 years after they received a clinical diagnosis of Parkinson's disease were randomly assigned to receive placebo or 3 to 12 mg of rivastigmine per day for 24 weeks. Primary efficacy variables were the scores for the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and Alzheimer's Disease Cooperative Study–Clinician's Global Impression of Change (ADCS-CGIC). Secondary clinical outcomes were the scores for the Alzheimer's Disease Cooperative Study Activities of Daily Living, the 10 item Neuropsychiatric Inventory, the Mini Mental State Examination, Cognitive Drug Research power of attention tests, the Verbal Fluency test, and the Ten Point Clock Drawing test. results A total of 541 patients were enrolled, and 410 completed the study. The outcomes were better among patients treated with rivastigmine than among those who received placebo; however, the differences between these two groups were moderate and similar to those reported in trials of rivastigmine for Alzheimer's disease. Rivastigmine treated patients had a mean improvement of 2.1 points in the score for the 70 point ADAS cog, from a baseline score of 23.8, as compared with a 0.7-point worsening in the placebo group, from a baseline score of 24.3 ($P<0.001$). Clinically meaningful improvements in the scores for the ADCS CGIC were observed in 19.8 percent of patients in the rivastigmine group and 14.5 percent of those in the placebo group, and clinically meaning-ful worsening was observed in 13.0 percent and 23.1 percent, respectively (mean score at 24 weeks, 3.8 and 4.3, respectively; $P=0.007$). Significantly better outcomes were seen with rivastigmine with respect to all secondary efficacy variables. The most frequent adverse events were nausea (affecting 29.0 percent of patients in the rivastigmine group and 11.2 percent of those in the placebo group, $P<0.001$), vomiting (16.6 and 1.7 per- cent, $P<0.001$), and tremor (10.2 and 3.9 percent, $P=0.01$). conclusions In this placebo controlled study, rivastigmine was associated with moderate improvements in dementia associated with Parkinson's disease but also with higher rates of nausea, vomiting, and tremor. (Murat Emre *et al*., 2008)

Suchowerksy *et al.* reported that to define key issues in the diagnosis of Parkinson disease (PD), to define features influencing progression, and to make evidence based recommendations. Which clinical features and diagnostic modalities distinguish PD from other parkinsonian syndromes? (2) Which clinical features predict rate of disease progression? Methods: Systematic review of the literature was completed. Articles were classified according to a four-tiered level of evidence scheme. Recommendations were based on the evidence.

RESULTS AND CONCLUSION

1. Early falls, poor response to levodopa, symmetry of motor manifestations, lack of tremor, and early autonomic dysfunction are probably useful in distinguishing other parkinsonian syndromes from Parkinson disease (PD).
2. Levodopa or apomorphine challenge and olfactory testing are probably useful in distinguishing PD from other parkinsonian syndromes.
3. Predictive factors for more rapid motor progression, nursing home placement, and shorter survival time include older age at onset of PD, associated comorbidities, presentation with rigidity and bradykinesia, and decreased dopamine responsiveness. Future research into methods for earlier and more accurate diagnosis of the disease and identification and clarification of predictive factors of rapid disease progression is warranted. (Suchowerksy *et al.,* 2006)

Pahwa *et al.* repoted that to make evidence-based treatment recommendations for the medical and surgical treatment of patients with Parkinson disease (PD) with levodopa induced motor fluctuations and dyskinesia. To that end, five questions were addressed.

1. Which medications reduce off time?
2. What is the relative efficacy of medications in reducing off time?
3. Which medications reduce dyskinesia?
4. Does deep brain stimulation (DBS) of the subthalamic nucleus (STN), globus pallidus interna (GPi), or ventral intermediate (VIM) nucleus of the thalamus reduce off time, dyskinesia, and antiparkinsonian medication usage and improve motor function?
5. Which factors predict improvement after DBS? Methods: A 10 member committee including movement disorder specialists and general neurologists evaluated the available evidence based on a structured literature review including MEDLINE, EMBASE, and Ovid databases from 1965 through June 2004.

1. Entacapone and rasagiline should be offered to reduce off time (Level A). Pergolide, pramipexole, ropinirole, and tolcapone should be considered to reduce off time (Level

B). Apomorphine, cabergoline, and selegiline may be considered to reduce off time (Level C).
2. The available evidence does not establish superiority of one medicine over another in reducing off time (Level B). Sustained release carbidopa/levodopa and bromocriptine may be disregarded to reduce off time (Level C).
3. Amantadine may be considered to reduce dyskinesia (Level C).
4. Deep brain stimulation of the STN may be considered to improve motor function and reduce off time, dyskinesia, and medication usage (Level C). There is insufficient evidence to support or refute the efficacy of DBS of the GPi or VIM nucleus of the thalamus in reducing off time, dyskinesia, or medication usage, or to improve motor function.
5. Preoperative response to levodopa predicts better outcome after DBS. (Pahwa *et al*., 2006)

Jennifer S.A.M Reijnders *et al*. reported that Prevalence rates of depressive disorders in Parkinson's disease (PD) vary widely across studies, ranging from 2.7% to more than 90%. The aim of this systematic review was to calculate average prevalences of depressive disorders taking into account the different settings and different diagnostic approaches of studies. Using Medline on Pubmed, a systematic literature search was carried out for studies of depression in Parkinson's disease. A total of 104 articles were included and assessed for quality; 51 articles ful lled the quality criteria. Multiple publications from the same database were not included in the meta-analysis. In the remaining 36 articles, the weighted prevalence of major depressive disorder was 17% of PD patients, that of minor depression 22% and dysthymia 13%. Clinically signi cant depressive symptoms, irrespective of the presence of a DSM de ned depressive disorder, were present in 35%. In studies using a (semi) structured interview to establish DSM criteria, the reported prevalence of major depressive disorder was 19%, while in studies using DSM criteria without a structured interview, the reported prevalence of major depressive disorder was 7%. Population studies report lower prevalence rates for both major depressive disorder and the clinically signi cant depressive symptoms than studies in other settings. This systematic review suggests that the average prevalence of major depressive disorder in PD is substantial, but lower than generally assumed. © 2007 Movement Disorder Society Key words: Parkinson's disease; depressive disorder; dysthymia; prevalence; systematic review. (Jennifer *et al*., 2007)

Cindy B. Levine *et al.* reported that Parkinson's Disease (PD) is estimated to affect over 1 percent of the population over age 65. The objective of this systematic review is to assess the quantity and quality of published evidence regarding diagnosis and treatment of patients with PD. English-language literature published from 1990 to 2000 was searched using electronic databases. Searches were supplemented by manually reviewing bibliographies of all accepted studies and selected review articles. Studies were required to evaluate at least 10 human patients and address predefined areas of interest. Only randomized controlled trials (RCTs) were accepted for studies regarding pharmacological treatment. Data Collection and Analysis. Pertinent data were evaluated for quality and level of evidence, extracted from accepted studies by one researcher, and reviewed by a second. Data were summarized and synthesized qualitatively. Meta-analyses were performed, comparing standardized mean changes from baseline to outcome in PD severity rating scales. The database includes 59 studies (3,369 patients) regarding diagnosis, 49 studies (9,968 patients) on pharmacological treatment, 42 studies (1,380 patients) on surgery, 10 studies (392 patients) on psychiatric treatment, and 20 studies (1,049 patients) on ancillary treatment of PD. PD is diagnosed clinically; evidence does not show that specific tests improve diagnostic accuracy. There is no evidence that different dopamine agonists (DAs) vary in treatment effects. Meta-analysis suggests that in early PD, treatment with DAs plus levodopa (L-dopa) may control PD symptoms better than treatment with L-dopa alone, but this was not a consistent finding. Similarly, no consistent difference in symptom control was found between L dopa alone and the combination therapy of L dopa plus selegiline. In patients with advanced disease, treatment with catechol O-methyl transferase (COMT) inhibitors combined with L dopa provides significantly greater PD symptom control than treatment with L-dopa alone and is associated with lower L dopa doses; however, long-term (greater than 7 months) results are lacking, and hepatotoxicity is a rare but potentially lethal side effect associated with tolcapone. For pallidotomy and deep brain stimulation (DBS), endpoint PD scale scores are significantly better than baseline scores. DBS of the subthalamic nucleus (STN) and globus pallidus (GPi) result in significant improvement in PD symptoms, but only STN DBS is associated with decreased L-dopa doses. There are insufficient studies of thalamotomy and tissue transplantation to draw any conclusions regarding their efficacy and safety. Ancillary treatments, such as physical therapy, improve some symptoms on a short-term basis, but long term data are lacking. Intensive speech therapy has been shown to improve vocal intensity up to 12 months after treatment; however, long-term results are from only one study of 22 patients. PD is diagnosed clinically; there is currently no gold standard premorbid diagnostic test for PD. Meta-analyses of different pharmacological treatments showed that the only medication that consistently controlled PD symptoms better than L dopa alone was the combination of L dopa plus COMT inhibitors in patients with advanced PD. Meta-analyses suggest that pallidotomy and DBS result in improvement of PD rating scores. The published literature regarding PD suffers from lack of reporting standardized outcomes. (Cindy.B.Levine *et al.,* 2003)

Michael W. Jakowec and Giselle M. Petzinger *et al.* reported that Animal models play a critical role in our understanding of the cause of human diseases and provide an opportunity to evaluate new therapeutic treatments. The usefulness of an animal model is dependent, in part, on how closely it resembles neurochemical, neuropathologic, and behavioral features of the human condition. Other considerations that may enhance the value of a model include expense, availability, reproducibility, animal morbidity and mortality, and investigator experience. Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by slow movements, tremor, and walking impairment due to loss of midbrain nigrostriatal neurons and depletion of striatal dopamine. In the PD research

field, a number of neurotoxic, pharmacologic, and transgenic animal models are available for research studies. We will focus on the advantages and disadvantages of the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) lesioned mouse and nonhuman primate models of PD. Our goal is to guide researchers in the appropriateness of the MPTP models in their studies by balancing understanding of the models, objectives of the study, and health and safety of the animals. In addition, the technical use and safe handling of MPTP are discussed. (Michael W. Jakowec *et al*., 2004

Nicholson *et al.* reported that Parkinson's disease is an increasingly common disease of elderly patients who present a particular anaesthetic challenge. This review explores the epidemiology, aetiology, pathogenesis, and pathophysiology of the condition, particularly the possible role of genetic factors. The clinical features are described in detail and recent advances in medical management are highlighted. Controversies surrounding the use of the newer drugs and possible advances in neurosurgical interventions are discussed. Particular anaesthetic problems in patients with Parkinson's disease are respiratory, cardiovascular, and neurological. Potential drug interactions are described and recommendations are made about suitable anaesthetic techniques. (Nicholson *et al.,* 2002)

Stanley Fahn and David Sulzer *et al.* reported that Many of the motoric features that de ne Parkinson disease (PD) result primarily from the loss of the neuromelanin (NM) containing dopamine (DA) neurons of the substantia nigra (SN), and to a lesser extent, other mostly catecholaminergic neurons, and are associated with cytoplasmic "Lewy body" inclusions in some of the surviving neurons. While there are uncommon instances of familial PD, and rare instances of known genetic causes, the etiology of the vast majority of PD cases remains unknown (i.e., idiopathic). Here we outline genetic and environmental ndings related to PD epidemiology, suggestions that aberrant protein degradation may play a role in disease pathogenesis, and pathogenetic mechanisms including oxidative stress due to DA oxidation that could underlie the selectivity of neurodegeneration. We then outline potential approaches to neuroprotection for PD that are derived from current notions on disease pathogenesis. Key Words: PARK genes, alpha synuclein, Parkin gene, ubiquitin pathway. (Stanley Fahn and David Sulzer, 2004)

Wenyu Fu, Wenxin Zhuang *et al.* reported that Parkinson's disease (PD) is one of the most common degenerative disorders of the central nervous system among the elderly. The disease is caused by the slow deterioration of the dopaminergic neurons in the substantia Nigra. Treatment strategies to protect dopaminergic neurons from progressive damage have received much attention. However there is no effective treatment for PD. Traditional Chinese medicines have shown potential clinical efficacy in attenuating the progression of PD. Increasing evidence indicates that constituents of some Chinese herbs include resveratrol, curcumin, and ginsenoside can be neuroprotective. Since pathologic processes in PD including inflammation, oxidative stress, apoptosis, mitochondrial dysfunction, and genetic factors lead to neuronal degeneration, and these Chinese herbs can protect dopaminergic neurons from neuronal degeneration, in this article, we review the neuroprotective roles of these herbs and summarize their anti-inflammatory, antioxidant, and anti-apoptotic effects in PD. In addition, we discuss their possible mechanisms of action in in vivo and in vitro models of PD. Traditional Chinese medicinal herbs, with their low toxicity and side effects, have become the potential therapeutic interventions for prevention and treatment of PD and other neurodegenerative diseases. (Wenyu *et al*., 2015)

Molly Foote, **Yi Zhou *et al.*** reported that 14-3-3 proteins were originally discovered as a family of proteins that are highly expressed in the brain. Through interactions with a multitude of binding partners, 14-3-3 proteins impact many aspects of brain function including neural signaling, neuronal development and neuroprotection. Although much remains to be learned and understood, 14-3-3 proteins have been implicated in a variety of neurological disorders based on evidence from both clinical and laboratory studies. Here we will review previous and more recent research that has helped us understand the roles of 14-3-3 proteins in both neurodegenerative and neuropsychiatric diseases. (Molly Foote *et al*., 2012)

Ludolpha *et al.* reported that Tauopathies with parkinsonism represent a spectrum of disease entities uni ed by the pathologic accumulation of hyperphosphorylated tau protein fragments within the central nervous system. These pathologic characteristics suggest shared pathogenetic pathways and possible molecular targets for disease-modifying therapeutic interven- tions. Natural history studies, for instance, in progressive supranuclear palsy, fronto temporal dementia with parkinsonism linked to chromosome 17, corticobasal degeneration, and Niemann Pick disease type C as well as in amyotrophic lateral sclerosis/Parkinson dementia complex permit clinical characterization of the disease phenotypes and are crucial to the development and validation of biological markers for di erential diagnostics and disease monitoring, for example, by use of neuro imaging or proteomic approaches. The wide pathologic and clinical spectrum of the tauopathies with parkinsonism is reviewed in this article, and perspectives on future advances in the understanding of the pathogenesis are given, together with potential therapeutic strategies. (Ludolpha *et al*., 2008)

Poewe *et al.* reported that Although still considered a paradigmatic movement disorder, Parkinsons disease (PD) is associated with a broad spectrum of non-motor symptoms. These include disorders of mood and a ect with apathy, anhedonia and depression, cognitive days function and hallucinosis, as well as complex behavioural disorders. Sensory dysfunction with hyposmia or pain is almost universal, as are disturbances of sleep wake cycle regulation. Auto nomic dysfunction including orthostatic hypotension, urogenital dysfunction and constipation is also present to some degree in a majority of patients. Whilst overall non motor symptoms become increasingly prevalent with advancing disease, many of them can also antedate the rst occurrence of motor signs most notably depression, hyposmia or rapid eye movement sleep behaviour disorder (RBD). Although exact clinic opathological correlations for most of these non-motor features are still poorly understood, the occurrence of constipation, RBD or hyposmia prior to the onset of clinically overt motor

dysfunction would appear consistent with the ascending hypothesis of PD pathology proposed by Braak and colleagues. Screening these early non motor features might, therefore, be one approach towards early preclinical diagnosis of PD. This review article provides an overview of the clinical spectrum of no -motor symptoms in PD together with a brief review of treatment options. (Poewe *et al.,* 2007)

Dorsey *et al.* reported that Based on published prevalence studies, we used two different methodologies to project the number of individuals with Parkinson disease (PD) in Western Europe's 5 most and the world's 10 most populous nations. The number of individuals with PD over age 50 in these countries was between 4.1 and 4.6 million in 2005 and will double to between 8.7 and 9.3 million by 2030. (Dorsey *et al*., 2005)

Elise Tandberg *et al.* reported that Sleep disorders are common and well documented in patients with Parkinson's disease (PD). However, most data on sleep in patients with PD are derived from selected patient populations. This community based survey evaluated the prevalence of and risk factors for sleep disturbances in an unselected group of 245 patients with PD and two control groups of similar age and sex distribution: 100 patients with another chronic disease (diabetes mellitus) and 100 healthy elderly persons. Nearly two thirds of the patients with PD reported sleep disorders, significantly more than among patients with diabetes (46%) and healthy control subjects (33%). About a third of the patients with PD rated their overall nighttime problem as moderate to severe. The most common sleep disorders reported by the patients with PD were frequent awakening (sleep fragmentation) and early awakening. Sleep initiation showed no significant difference compared with the control groups. Pain and cramps were not more prevalent among the patients with PD, but they were more likely to report sleep disturbed by myoclonic jerks. Use of sedatives was common in all three groups but significantly higher in the PD group than in the healthy elderly. Symptoms of depression and duration of levodopa treatment showed a significant correlation with sleep disorders in the PD group. This community based study confirms that sleep disorders are common and distressing in patients with PD. The strong correlation between depression and sleep disorders in patients with PD underlines the importance of identifying and treating both conditions in these patients. (Elise Tandberg *et al*., 2004)

William Langston *et al.* reported that It is suggested here that in most cases of Parkinson's disease the cause may be an environmental factor, possibly toxic, superimposed on a background of slow, sustained neuronal loss due to advancing age. (William Langston *et al.,* 1983)

Jaswinder Sian *et al.* reported that Reduced glutathione (GSH) and oxidized glutathione (GSSG) levels were measured in various brain areas (substantia nigra, putamen, caudate nucleus, globus pallidus, and cerebral cortex) from patients dying with Parkinson's disease, progressive supranuclear palsy, multiple system atrophy, and Huntington's disease and from control subjects with no neuropathological changes in substantia nigra. GSH levels were reduced in substantia Nigra in Parkinson's disease patients (40% compared to control subjects) and GSSG levels were marginally (29%) but insignificantly elevated; there were no changes in other brain areas. The only significant change in multiple system atrophy was an increase of GSH (196%) coupled with a reduction of GSSG (60%) in the globus pallidus. The only change in progressive supranuclear palsy was a reduced level of GSH in the caudate nucleus (51%). The only change in Huntington's disease was a reduction of GSSG in the caudate nucleus (50%). Despite profound nigral cell loss in the substantia nigra in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy, the level of GSH in the substantia nigra was significantly reduced only in Parkinson's disease. This suggests that the change in GSH in Parkinson's disease is not solely due to nigral cell death, or entirely explained by drug therapy, for multiple-system atrophy patients were also treated with levodopa. The altered GSH/GSSG ratio in the substantia nigra in Parkinson's disease is consistent with the concept of oxidative stress as a major component in the pathogenesis of nigral cell death in Parkinson's disease. (Jaswinder Sian *et al*., 1994)

Roger Belizaier *et al.* reported that Parkinson's disease (PD) is characterized pathologically by preferential degeneration of the dopaminergic neurons in the substantia nigra pars compacta (SNc). Nigral cell death is accompanied by the accumulation of a wide range of poorly degraded proteins and the formation of proteinaceous inclusions (Lewy bodies) in dopaminergic neurons. Mutations in the genes encoding α-synuclein and two enzymes of the ubiquitin proteasome system, parkin and ubiquitin C-terminal hydrolase L1, are associated with neurodegeneration in some familial forms of PD. We now show that, in comparison to age matched controls, α-subunits (but not β-subunits) of 26/20S proteasomes are lost within dopaminergic neurons and 20S proteasomal enzymatic activities are impaired in the SNc in sporadic PD. In addition, while the levels of the PA700 proteasome activator are reduced in the SNc in PD, PA700 expression is increased in other brain regions such as the frontal cortex and striatum. We also found that levels of the PA28 proteasome activator are very low to almost undetectable in the SNc compared to other brain areas in both normal and PD subjects. These findings suggest that failure of the ubiquitin proteasome system to adequately clear unwanted proteins may underlie vulnerability and degeneration of the SNc in both sporadic and familial PD. (Roger Belizaire *et al.,* 2003)

Olanow *et al.* reprted that Iron-induced oxidant stress has been implicated in the pathogenesis of Parkinson's disease. An increasing body of evidence now indicates that in Parkinson's disease the environment within the substantia nigra is conducive to the formation of cytotoxic free radicals and cell degeneration. Dopamine neurons may be particularly vulnerable because of the oxidative metabolism of dopamine and the potential of neuromelanin to promote the site-specific accumulation and reduction of iron. This hypothesis has attracted considerable attention because it opens the way for employing antioxidant strategies as possible neuroprotective treatment for Parkinson's disease. Although the concept is appealing, free radicals have not yet been proven to play a role in Parkinson's disease, and many important issues remain to be resolved before the oxidative hypothesis can ultimately be confirmed or refuted. (Olanow *et al.,* 2004)

Mitsuru Shiba *et al.* reported that the association between preceding psychiatric disorders and Parkinson's disease (PD) using a case-control design. We used the medical records-linkage system of the Rochester Epidemiology Project to identify 196 subjects who developed PD in Olmsted County, Minnesota, during the years 1976–1995. Each case was matched by age (±1 yr) and sex to a general population control. We reviewed the complete medical records of cases and control subjects to detect preceding psychiatric disorders. The frequency of psychiatric disorders was higher in cases than in control subjects; the odds ratio was 2.2 for anxiety disorders (95% confidence interval (95% CI) = 1.4–3.4; p = 0.0003), 1.9 for depressive disorders (95% CI = 1.1–3.2; p = 0.02), and 2.4 for both anxiety disorders and depressive disorders occurring in the same individual (95% CI = 1.2–4.8; p = 0.02). When we restricted analyses to disorders present 5 years or more before the onset of motor symptoms of PD, the association with depressive disorders lost statistical significance. However, the association with anxiety disorders remained significant for disorders present 5, 10, or 20 years before onset of motor symptoms. Our results suggest that anxiety disorders and depressive disorders are associated with PD and that the causative process or the risk factors underlying PD are present many years before the appearance of motor symptoms. (Mitsuru Shiba *et al*., 2001)

Dexter *et al.* reported that Polyunsaturated fatty acid (PUFA) levels (an index of the amount of substrate available for lipid peroxidation) were measured in several brain regions from patients who died with Parkinson's disease and age-matched control human postmortem brains. PUFA levels were reduced in parkinsonian substantia nigra compared to other brain regions and to control tissue. However, basal malondialdehyde (MDA; an intermediate in the lipid peroxidation process) levels were increased in parkinsonian nigra compared with other parkinsonian brain regions and control tissue. Expressing basal MDA levels in terms of PUFA content, the difference between parkinsonian and control substantia nigra was even more pronounced. Stimulating MDA production by incubating tissue with $FeSO_4$ plus ascorbic acid, $FeSO_4$ plus H_2O_2, or air alone produced lower MDA levels in the parkinsonian substantia nigra, probably reflecting the lower PUFA content. These results may indicate that an increased level of lipid peroxidation continues to occur in the parkinsonian nigra up to the time of death, perhaps because of continued exposure to excess free radicals derived from some endogenous or exogenous neurotoxic species. (Dexter *et al.,* 2006)

Jeffrey *et al.* reported that As part of a safety and tolerability study, a 65 year-old man with Parkinson's disease (PD) received monthly intracerebro-ventricular injections of glial-derived neurotrophic factor (GDNF). His Parkinsonism continued to worsen following intracerebro-ventricular GDNF treatment. Side effects included nausea, loss of appetite, tingling, L'hermitte's sign, intermittent hallucinations, depression, and inappropriate sexual conduct. There was no evidence of significant regeneration of nigrostriatal neurons or intraparenchymal diffusion of the intracerebroventricular GDNF to relevant brain regions. Alternative GDNF delivery systems should be explored. (Jeffrey *et al*., 2001)

Riedel *et al.* reported that Parkinson's disease (PD) is often accompanied by non-motor complications, such as dementia, depression, and psychotic symptoms, which worsen the prognosis and increase the personal and socioeconomic burden of disease. Prevalence estimates of these complications are quite variable and are lacking for the outpatient care sector. As part of a larger, nationwide, cross sectional epidemiological study in n = 315 neurological outpatient settings in Germany, this paper estimates the frequency of dementia and cognitive impairment in n = 873 outpatients meeting the UK Brain Bank criteria for idiopathic PD. Assessments were based on a clinical interview and neuropsychological assessments, including the Hoehn & Yahr rating and Unified Parkinson's Disease Rating Scale (UPDRS). Cognitive impairment was assessed by the Mini Mental State Exam (MMSE), Clock Drawing Test (CDT) and the Parkinson Neuropsychometric Dementia Assessment (PANDA) and the clinician's diagnosis of dementia was based on the diagnostic criteria of DSMIV. Using standardized cutoff scores, the prevalence of cognitive impairment in the study sample as measured by various methods was 17.5% by MMSE (≤ 24), 41.8% by CDT (≥ 3), 43.6% by PANDA (≤ 14), and 28.6% met the DSM-IV criteria for dementia. All estimates increased with age and PD severity. Gender was an inconsistent contributor while illness duration had no significant impact on cognition. Multiple regression analyses revealed PD severity to be the strongest predictor of dementia risk (OR = 4.3; 95% CI: 2.1–9.1), while neuropsychiatric syndromes had independent, although modest additional contributions (OR = 2.5, 95% CI: 1.6–3.8). Estimates of cognitive impairment and dementia in PD patients are largely dependent on the diagnostic measure used. Using established clinical diagnostic standards for dementia the overall rate on routine outpatient neurological care is 28.6%, but using more sensitive neuropsychological measures, rates for cognitive impairment might be up to 2-fold higher. The MMSE revealed strikingly low sensitivity. Neuropsychiatric syndromes, in addition to PD severity and age, have an independent although modest additional contribution to patients' risk for cognitive impairment and dementia. (Riedel *et al.,* 2008)

Hartley *et al.* reported that the mode of cell death in Parkinson's disease (PD) substantia nigra is uncertain. However, evidence is accumulating that certain of the biochemical abnormalities present in PD nigra at the time of death may precipitate apoptosis. We have investigated the mode of death induced by complex I inhibition of dopaminergic cell cultures, and our results suggest that both 1-methyl-4-phenylpyridinium and rotenone cause apoptosis at low concentrations and necrosis at high concentrations. This dose dependent shift in the mode of cell death induced by these mitochondrial toxins may have important implications for the mechanism of neuronal cell death in PD. (Hartley *et al.,* 2002)

Haken Widner *et al.* reported that in 1992 the Core Assessment Program for Intracerebral Transplantations (CAPIT) was published providing the minimal requirements for a common patient evaluation protocol. Despite the intent, the program was thought to be too laborious to carry out in large scale trials, and it also lacked evaluations of cognitive functions and quality of life. Moreover, the CAPIT was

designed for neural transplantation only and has not been revised since. Since then, pallidotomy and deep brain stimulation have emerged as additional treatment modalities but there exists no common tool for evaluation of, and between, the techniques. In 1996, within the framework of NECTAR (Network for European CNS Transplantation and Restoration), a dedicated program entitled "Neurosurgical Interventions in Parkinson's Disease" (NIPD) was funded by the European Union Biomed 2 program to develop a new Core Assessment Program for Surgical Interventional Therapies in PD (CAPSIT-PD) and to establish an European registry for patients with PD subjected to functional neurosurgery. This article presents the recommendations of this new program. (**Haken Widner *et al.*, 2001**)

Smith *et al.* reported that the pathogenesis of Parkinson's disease may be influenced by genetic and environmental factors. Cytochrome P450 mono-oxygenases help to protect against toxic environmental compounds and individual variations in cytochrome P450 expression might, therefore, influence susceptibility to environmentally linked diseases. The frequency of mutant CYP2D6 alleles was studied in 229 patients with Parkinson's disease and 720 controls. Individuals with a metabolic defect in the cytochrome P450 CYP2D6 debrisoquine hydroxylase gene with the poor metaboliser phenotype had a 2·54-fold (95% Cl 1·51-4·28) increased risk of Parkinson's disease. Determination of CYP2D6 phenotype and genotype may help to identify those at greatest risk of Parkinson's disease and may also help to identify the environmental or metabolic agents involved in the pathogenesis of this disease. (Smith *et al*., 1992)

Jeffrey *et al.* reported that Parkinson's disease (PD) is a disabling neurodegenerative condition commonly complicated by the existence of comorbid depression. The prevalence rates of depression in this patient group have been reported to be as high as 40%. Currently, depression in PD is undertreated; there have been few controlled clinical trials of antidepressants in this patient group. Patients with PD are usually elderly and often administered a range of medication, therefore the choice of antidepressant must be undertaken with care. Tricyclic antidepressants (TCAs) have been studied in patients with PD and comorbid depression; however, the risk of anticholinergic side effects means that their use is largely avoided. Selective serotonin reuptake inhibitors have comparable efficacy to the TCAs and a better tolerability profile in patients with depression; they are rapidly being considered as first-line therapy for PD patients with depression. Clinical studies in this patient group are warranted. This article reviews the characteristics of comorbid depression in patients with PD and discusses the treatment options available**. (**Jeffrey *et al.,* 1999**)**

Brooks *et al.* reported that Using positron emission tomography (PET), regional striatal F dopa uptake in 16 patients with L dopa responsive Parkinson's disease (PD), 18 patients with multiple system atrophy, and 10 patients with progressive supranuclear palsy. Results were compared with those of 30 age matched normal volunteers. The patients with PD showed significantly reduced mean uptake of F dopa in the caudate and putamen compared to controls, but while function in the posterior part of the putamen was severely impaired (45% of normal), function in the anterior part of the putamen and in the caudate was relatively spared (62% and 84% of normal). Mean F dopa uptake in the posterior putamen was depressed to similar levels in all patients. Unlike patients with PD, the patients with progressive supranuclear palsy showed equally severe impairment of mean F dopa uptake in the anterior and posteior putamen. Caudate F dopa uptake was also significantly lower in patients with progressive supranuclear palsy than in patients with PD, being depressed to the same level as that in the putamen. Mean F dopa uptake values in the anterior putamen and caudate in patients with multiple system atrophy lay between PD and progressive supranuclear palsy levels. Locomotor disability of individual patients with PD or multiple system atrophy correlated with decline in striatal F dopa uptake, but this was not the case for the patients with progressive supranuclear palsy. We conclude that patients with PD have selective nigral pathological features with relative preservation of the dopaminergic function in the anterior putamen and caudate, whereas there is progressively more extensive nigral involvement in multiple system atrophy and progressive supranuclear palsy. If an akinetic rigid patient has equally depressed ^{18}F-dopa uptake in the caudate and putamen, that person is likely to have neuropathological changes other than those of idiopathic PD. (Brooks *et al.,* 2004)

Lozano *et al.* reported that the major motor disturbances in Parkinson's disease are thought to be caused by overactivity of the internal segment of the globus pallidus (GPi), in large part due to excessive drive from the subthalamic nucleus. The excessive inhibitory activity of GPi is thought to "brake' the motor thalamus and the cortical motor system to produce the slowness, rigidity, and poverty of movement characteristic of parkinsonian states. To test the hypothesis that direct reduction of Gpi activity can improve motor function, we studied the effect of GPi pallidotomy in 14 patients. The location of the GPi nucleus was confirmed by microelectrode recording before lesion creation. Standardised videotape recordings before and after operation were randomised and scored by a "blinded' evaluator. 6 months after surgery, total motor score in the "off" state had improved by 30% and the total akinesia score by 33%. The gait score in the "off" state improved by 15% and a composite postural instability and gait score by 23%. After surgery there was almost total elimination of drug-induced involuntary movements (dyskinesias), with a 92% reduction on the side contralateral to the pallidotomy. No patient had visual or corticospinal complications. (Lozano *et al.,* 1995)

Edwards *et al.* reported that the prevalence of gastrointestinal (GI) symptoms in 98 individuals with Parkinson's disease (PD) and in a control group of 50. Seventy-nine of those with PD were being treated with dopaminergic medications and 19 were untreated. Those symptoms occurring more frequently in PD patients than in controls included abnormal salivation, dysphagia, nausea, constipation, and defecatory dysfunction. Except for defecatory dysfunction, symptoms did not correlate with treatment but instead correlated with disease severity. This suggests that the GI symptoms of PD reflect direct involvement in the GI tract by the primary disease process**.** (Edwards *et al.,* 2004)

Boka *et al.* reported that activated glial cells observed in the substantia nigra in Parkinson's disease may participate in the mechanism of nerve cell death by producing toxic substances such as cytokines. Among these compounds, tumor necrosis factor-α (TNF) is of interest because it can provoke cell death. We detected TNF-immunoreactive glial cells in the substantia nigra of parkinsonian patients but not in those of control subjects. Immunoreactivity for TNF receptors was found in cell bodies and processes of most dopaminergic neurons of control and parkinsonian subjects, suggesting that nigral dopaminergic neurons might be sensitive to TNF produced in Parkinson's disease. These results suggest that TNF may participate in the degenerative processes occurring in Parkinson's disease, at least after a primary insult inducing a reactive gliosis **(Boka *et al.*, 1994*)***

Nail Quinn *et al.* reported that a personal series of 60 cases of parkinsonism with onset under the age of 40 years. Known causes for early onset of secondary parkinsonism, such as Wilson's disease or encephalitis, were excluded in every case. Two groups were identified: those with onset after the age of 21 in whom no hereditary factors could be ascertained (56 cases), and those with onset before 21 years all of whom had familial parkinsonism. In neither group have we found any association with prematurely grey hair, hypertension, diabetes, pernicious anaemia, or thyroid disorder. Among their families, we have not found any association with diabetes, pernicious anaemia, or thyroid disorder. We propose that cases of apparent idiopathic Parkinson's disease begining between age 21–40 years should be called "young onset Parkinson's disease." Twenty percent of such patients in our series had at least one first- or second-degree relative in the same or antecedent generations with parkinsonism, but only 1.5% of their relatives at risk had parkinsonism, which is similar to the prevalence in the general population. Ten percent of these patients had at least one relative with essential tremor, but only 1.6% of their relatives at risk had tremor, which again was similar to the prevalence in the population in general. These patients with young onset Parkinson's disease responded well to levodopa therapy. However, dyskinesias and response fluctuations occurred early and frequently. The prevalence of dyskinesias and response fluctuations was strongly correlated with the duration of levodopa treatment, but not with the duration (or probably the severity) of the disease before levodopa therapy was commenced. The involuntary movements often were severe and frequently were diphasic. Despite long disease duration, the incidence of dementia in young onset patients aged less than 65 years was negligible. We believe that most, if not all, patients in this group have degenerative Lewy body idiopathic Parkinson's disease, representing the lower end of a skewed deviation for age of onset of this disease. We have so far failed to identify any additional environmental factor which may have accelerated disease onset in these patients. In contrast, cases of parkinsonism beginning before age 21 years were invariably familial. We proposed that they should be called "juvenile parkinsonism." All affected relatives with parkinsonism also had young disease onset, and all but one were siblings. None of four such patients seen has demented, and computed tomography (CT) scan has been normal in all four. It believed that most such patients have some form of genetically determined secondary parkinsonism. (Nail Quinn *et al.,* 2004)

Anne-Maria Kuopio *et al.* reported that The objective of this study was to examine the quality of life in patients with Parkinson's disease (PD) in a community-based sample (n = 228 patients) using a Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) as a measure. Associations to the variables age, age at onset, duration, clinical stage (Hoehn and Yahr), depression (Zung), and dementia (MMSE) were studied. Women scored significantly lower on five of the eight dimensions of SF-36. Depression, as measured in this study, was more common among parkinsonian women than men. Depression was the factor that was associated most significantly with the experienced quality of life, according to SF-36. With physical functioning, only the clinical stage had a more significant association than depression. To improve the quality of life in patients with PD, it is necessary to make every effort to recognize and relieve the depression of patients with PD. (Anne-Maria Kuopio *et al.,* 2001)

Zweig *et al.* reported that the study demonstrated a significant loss of neurons within the lateral part of the pedunculoponite nucleus pars compacta in individuals with idiopathic Parkinson's disease and in individuals with combined Parkinson's and Alzheimer's disease. We also examined the extent of neuronal loss within the substantia nigra pars compacta, locus ceruleus, dorsal raphe nucleus, and nucleus basalis of Meynert. The number of pedunculopontine nucleus pars compacta neurons in the patients with Parkinson's or Parkinson's and Alzheimer's disease was reduced (average, 40°) in comparison with the number in control subjects or patients with Alzheimer's disease ($p < 0.01$). This finding correlated significantly with the extent of loss of substantia nigra pars compacta neurons ($p < 0.01$). (Zweig *et al.,* 2004)

Thaut *et al.* reported that Rhythmic auditory stimulation (RAS) was used as a pacemaker during a 3-week home-based gaittraining program for Parkinson's disease (PD) patients (n = 15). Electromyogram (EMG) patterns and stride parameters were assessed before and after the test without RAS to evaluate changes in gait patterns. Data were compared with those of two control groups (n = 11), who either did not participate in any gait training or who participated in an internally self-paced training program. RAS consisted of audiotapes with metronome-pulse patterns embedded into the on/off beat structure of rhythmically accentuated instrumental music. Patients who trained with RAS significantly ($p < 0.05$) improved their gait velocity by 25%, stride length by 12%, and step cadence by 10% more than self-paced subjects who improved their velocity decreased by 7% and no-training subjects whose velocity decreased by 7%. In the RAS-group, timing of EMG patterns changed significantly ($p < 0.05$) in the anterior tibialis and vastus lateralis muscles. Evidence for rhythmic entrainment of gait patterns was shown by the ability of the RAS group to reproduce the speed of the last training tape within a 2% margin of error without RAS. (Thaut *et al.,* 2004)

Jillinger *et al.* reported thatReduced and oxidized glutathione concentrations in post-mortem brain tissue from the substantia nigra of control subjects and patients with neuropathologically confirmed Parkinson's disease were measured by a coulometric method using high-pressure liquid chromatography and

electrochemical detection. Reduced glutathione concentrations were decreased in the substantia nigra of parkinsonian patients compared with controls. Differences in the concentration of oxidized glutathione and in the percentage of oxidized glutathione of the total glutathione were not observed between parkinsonian and control subjects. The finding that oxidized glutathione is not decreased in Parkinson's disease suggests that the decrease in reduced glutathione is not exclusively the consequence of neuronal loss in the substantia nigra but may indicate a state of oxidative stress (Jillinger *et al.,* 2003).

Hallett *et al.* reported that comparision between procedural learning, translation of procedural knowledge into declarative knowledge, and use of declarative knowledge in age-matched normal volunteers (n = 30), patients with Parkinson's disease (n = 20), and patients with cerebellar degeneration (n = 15) by using a serial reaction time task. Patients with Parkinson's disease achieved procedural knowledge and used declarative knowledge of the task to improve performance, but they required a larger number of repetitions of the task to translate procedural knowledge into declarative knowledge. Patients with cerebellar degeneration did not show performance improvement due to procedural learning, failed to achieve declarative knowledge, and showed limited use of declarative knowledge of the task to improve their performance. Both basal ganglia and cerebellum are involved in procedural learning, but their roles are different. The normal influence of the basal ganglia on the prefrontal cortex may be required for timely access of information to and from the working memory buffer, while the cerebellum may index and order events in the time domain and be therefore essential for any cognitive functions involving sequences. (Hallett *et al.* 2004)

Franois Boller *et al.* reported thatClinical records and neuropathological specimens from 36 patients with autopsy-demonstrated idiopathic Parkinson disease (PD) were reviewed independently and the results compared. Nine (31%) of the 29 patients with adequate clinical data had severe dementia and 7 (24%) had mild dementia. The cerebral cortex showed senile plaques and fibrillary tangles in 15 of the 36 patients (42%). These changes were found in all 9 patients with severe dementia, in 3 of the 7 with mild dementia, and in 3 of the 13 patients with normal mental status. The prevalence of pathologically established Alzheimer changes and dementia among the patients with PD (33%) was over six times that found in an age-matched population (5.1%). Survival after the onset of PD with Alzheimer disease was shorter than in PD without Alzheimer disease. (Franois Boller *et al.,* 2004)

Copper *et al.* reported that The structure and function of mitochondrial respiratory-chain enzyme proteins were studied postmortem in the substantia nigra of nine patients with Parkinson's disease and nine matched controls. Total protein and mitochondrial mass were similar in the two groups. NADH-ubiquinone reductase (Complex I) and NADH cytochrome **c** reductase activities were significantly reduced, whereas succinate cytochrome **c** reductase activity was normal. These results indicated a specific defect of Complex I activity in the substantia nigra of patients with Parkinson's disease. This biochemical defect is the same as that produced in animal models of parkinsonism by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and adds further support to the proposition that Parkinson's disease may be due to an environmental toxin with action(s) similar to those of MPTP. (Copper *et al.,* 2006)

Chong *et al.* reported that Clinical symptoms of Parkinson's disease (PD) do not manifest until dopamine (DA) neuronal loss reaches a symptomatic threshold. To explore the mechanisms of functional compensation that occur in presynaptic DA nerve terminals in PD, we compared striatal positron emission tomographic (PET) measurements by using (^{11}C)dihydrotetrabenazine ((^{11}C)DTBZ; labeling the vesicular monoamine transporter type 2), (^{11}C)methylphenidate (labeling the plasma membrane DA transporter), and (^{18}F)dopa (reflecting synthesis and storage of DA). Three consecutive PET scans were performed in three-dimensional mode by using each tracer on 35 patients and 16 age-matched, normal controls. PET measurements by the three tracers were compared between subgroups of earlier and later stages of PD, between drug-naive and drug-treated subgroups of PD, and between subregions of the parkinsonian striatum. The quantitative relationships of (^{18}F)dopa and (^{11}C)DTBZ, and of (^{11}C)methylphenidate and (^{11}C)DTBZ, were compared between the PD and the normal control subjects. We found that (^{18}F)dopa $\mathbf{K}_i$ was reduced less than the binding potential ($\mathbf{B}_{max}/\mathbf{K}_d$) for (^{11}C)DTBZ in the parkinsonian striatum, whereas the (^{11}C)methylphenidate binding potential was reduced more than (^{11}C)DTBZ binding potential. These observations suggest that the activity of aromatic L-amino acid decarboxylase is up-regulated, whereas the plasma membrane DA transporter is down-regulated in the striatum of patients with PD. (Chong *et al.,* 2001)

DISCUSSION

1: The MPTP lesioned mouse and nonhuman primate models of basal ganglia injury are valuable in understanding the pathophysiology of PD and play an important role in developing and testing new therapeutic modalities. The lesioning regimen and species used result in different degrees of cell loss, dopamine depletion, and motor behavior deficits. Each model has its own advantages and disadvantages, depending on the scientific questions under investigation. Since humans lesioned with MPTP manifest clinical symptoms identical to those associated with idiopathic PD and progress on the basis of neuropathologic changes and PET imaging studies, this supports the fact that MPTP provides an excellent tool to generate a model that replicates PD. Much of our understanding of PD in humans comes from the analysis of late stage disease (when brains become available). Since we are able to investigate MPTP lesioned animals early, during, and in a time course manner after lesioning in a variety of species and lesioning severities, it forces us to reconsider our understanding of the human disease. New findings in the MPTP lesioned animal models continuously guide researchers to address hypotheses for the human condition. The MPTP is a valuable research tool, and although it is a potent neurotoxin, it can be used safely taking into consideration procedures to protect research investigators. In addition, other animal models, including those generated by use of various neurotoxic compounds, such as 6 hydroxydopamine, rotenone, or

methamphetamine, and newly developed transgenic and spontaneous mutant models, add to our arsenal of scientific tools. It is important that new thera peutic strategies for PD, such as pharmacologic agents, engineered vectors, stem cells, or noninvasive interventions, be fully evaluated in animal models prior to their introduction to the clinical setting. These scientific goals must be balanced with measures to reduce the number of animals used and to minimize potential animal pain, distress, and discomfort.

2: The efforts to understand the precise pathway by which neurodegenerative processes proceed and the development of approaches to modulate them offers the promise to eventually enable the prevention of these diseases. So far, no medication or surgical approach has been accepted as having been proven to be neuroprotective in PD. But with so much new knowledge on patho genesis and genetic mechanisms having been presented in the last few years, there are now new ideas on drugs that could be tested in clinical trials. As mentioned above, some of these trials are already underway. Others are in the planning stages, and still others are only being contemplated. One problem is whether there are enough early stage patients available to be enrolled into the proposed trials. There must be enough nancial resources available. It would be best to have a priority of agents to be tested based on the most likely to be successful. Fortunately, the National Institute of Neurological Diseases and Stroke (NINDS) have already established an Oversight Committee to guide the Institute in this type of strategy. Enthusiasm is high; let the studies begin

3: The HY scale is a widely used clinical rating scale, describing broad categories of motor dysfunction in PD. Among its advantages is that it is simple and applied easily. It captures typical patterns of PD progression with and without dopaminergic therapy. Progression in HY stage correlates with motor decline and deterioration in quality of life. The limited clinimetric analyses conducted to date support its scienti c and clinical credibility. On the other hand, because of its simplicity, the scale is not comprehensive and by focusing on the issues of unilateral versus bilateral disease and the presence or absence of postural re ex impairment, it leaves other aspects of PD unassessed. By combining disability and impairment, ambiguities exist, and all clinical presentations of PD are not covered. The broad categories of the scale do not permit consistent detection of effective interventions, and the establishment of MCRD and MCRID indices is not feasible. Attempts to rectify weaknesses have included the introduction of widely used 0.5 increments to the scale, but this adaptation has not been tested clinimetrically and introduces unresolved analytic problems. Although still used frequently as an outcome measure in clinical trials, the HY scale has been replaced largely by the UDPRS as a primary outcome measure of treatment ef cacy. Time to the development of a given HY stage has been used successfully to distinguish patients with PD from other parkinsonism plus syndromes, and this measure could be potentially incorporated into interventional studies designed to test delay in clinical progression.

4: A systematic review that assessed the efficacy and safety of acupuncture therapy (monotherapy or adjuvant therapy), compared with placebo, conventional interventions, or no treatment in treating patients with idiopathic Parkinson's disease. Ten randomised controlled trials were included, each using a different set of acupoints and manipulation of needles. Nine of the trials claimed a statistically significant positive effect from acupuncture as compared with their control; only one indicated that there were no statistically significant differences for all variables measured. Only 2 studies described details about adverse events. The reviewers concluded that there is evidence indicating that acupuncture may be effective for treating idiopathic Parkinson's disease. However, they stated that the results were limited by methodological flaws in the studies, and missing information about allocation concealment, number of dropouts, and blinding methods.

5: Parkinson's disease results from a gradual loss of neurons that produce dopamine. This causes an imbalance in the brain leading to symptoms of tremor, gait problems and cognitive decline. Diagnosis is made on clinical grounds and treatment is typically through oral medication intended to replace dopamine. As disease severity worsens and side effects of medication become exceedingly worse, more radical therapies such as deep brain stimulation and surgical lesioning are explored. Continued scientific research into Parkinson's disease may reveal important clues to help find more effective treatments in the near future.

6: The summarized published clinical evidence that lends support to the use of therapeutic interventions for Parkinson's disease. The assessment panel recognises that its conclusions are constrained by some factors. Inclusion criteria to incorporate trials into the review process were restrictive. Publication practices bias toward reports with favourable results. The database analysis was closed in January, 2001, and it is expected that more recently published trials and future randomised controlled trials will permit modifications of conclusions in this ongoing effort, especially those relating to recent interventions. The few trials identified with the older medications, such as anticholinergics, amantadine, and the first generation of dopamine agonists, were done in times when technical solutions to plan such trials had not yet developed. Since then, those drugs have come off patent, and there is no present financial interest in understanding them better. Consequently, conclusions on efficacy are better substantiated for recently marketed drugs than for older ones, though the stronger conclusions might not reflect true clinical differences. Conversely, years of experience with an older agent offers greater reliability with respect to safety than does the short follow up of recent agents. Throughout this review, conclusions were more focused on proof of efficacy than safety, because reviewing randomised controlled trials is not the best method to study side effects, especially the less frequent ones.

7: Idiopathic Parkinsonism is inherently a progressive disorder, but the progression can be very slow. In distinguishing idiopathic Parkinson's disease from other Parkinsonian syndromes, asymmetry of clinical deficits may be helpful. Although it is true that IP is always asymmetrical in its early stages, unequal disturbances on each side is frequently encountered in other Parkinsonian syndromes. The diagnostic criteria which have been subjected to reliability and validation studies include: (1) the presence of at least 1 year of 2 of the

following cardinal motor signs: resting/postural tremor; bradykinesia and rigidity. (2) Responsiveness to levodopa therapy. Different forms of Parkinson's disease occur in varying percentages in a group of patients, primarily idiopathic, vascular, drug- induced, and hereditary Parkinsonism The first diagnostic criterion does not take into account postural instability, which occurs in many of the Parkinson plus syndrome and advanced PD. The second criterion is not sufficient by itself to diagnose PD. Other Parkinsonian states have a mild to moderate response to levododopa therapy, although the effect is often transient.

8: Four years from baseline, 7% of the individuals with idiopathic olfactory loss had newly developed clinical IPD symptoms, and altogether, 13% of the patients presented with IPD relevant abnormalities of the motor system. As compared to an IPD prevalence of 1.6 % in the general European population,19 and of 1.8 to 2.6% in the elderly, 20 our results support previous data8 indicating that olfactory loss is indeed of prognostic value with respect to IPD symptoms. Agreement with pathological UPDRS scores was observed in two of seven abnormal SPECT results, and in three of 11 abnormal TCS ndings, whereas the numbers of "false negatives" normal results as opposed to pathological UPDRS scores were two among SPECT, and one among TCS data. The incomplete matrix of procedures performed in this study has to be taken into account, limiting the range of conclusions. However, our data obtained so far suggest that a combination of olfactory testing and an additional TCS or SPECT examination may constitute a promising screening tool. Another aspect of SPECT scans with regard to presymptomatic IPD concerns the time course of decline of activation indicated by dopaminergic markers. This has been estimated to approximate an annual rate of 7 to 9%. Thus, it relates to the thresholds at which de cits become detectable by SPECT and motor symptoms become clinically signi cant. Possibly, olfactory dysfunction antedates the reaching of both, as Braak *et al*. observed the neuropathological alterations associated with IPD to occur earliest in the anterior olfactory nucleus (and dorsal motor nuclei of cranial nerves IX and X). Why was olfactory loss not identi ed in the careful study by Marras *et al*. as an early marker of IPD? As mentioned in the Introduction, they observed that none of their patients developing IPD over a 7 year period had initially exhibited olfactory loss. However, as pointed out by the authors themselves, the reason for this negative nding might lie in the very long observation period of 7 years, which may have been too early for their subjects to have yet developed signs of smell dysfunction. In conclusion, the present results indicate that unexplained olfactory loss may be associated with an increased risk of developing IPD relevant motor symptoms. Although further work, preferably with larger samples and more sophisticated study designs will be needed to assess in detail feasible and effective ways of IPD screening, olfactory loss should be considered a promising contribution to the diagnosis of early IPD.

Although genes that are linked to monogenic forms of Parkin's disease aand other closely related neurodegenerative diseases are,at first glance, not related to a cooman cause, recent genetic, pathologic and molecular studies have strengthened the evidence that there is probably more "cross talk" between the different pathway, on several levels, then previously appreciated. These finding support the existance of common pathogenic mechanisms, protein aggregiation, mitochondrial dysfunction or oxidative stress, which had been suspectd as major culprits of neurodegeneration for many years. This review tries to demonstrates that during routine office visits, neurologist failed to identify the presence of depression, anxiety, and fatigue more than half of the time failed to recognize sleep disturbance in 40% of patients. Awareness of likelihood under recognition of behavioral symptoms in PD should generate approaches to diagnostic accuracy and facilitate timely therapeutic interventions.

Concludatory Comments

The efforts to understand the precise pathway by which neurodegenerative processes proceed and the development of approaches to modulate them offers the promise to eventually enable the prevention of these diseases. So far, no medication or surgical approach has been accepted as having been proven to be neuroprotective in PD. But with so much new knowledge on patho- genesis and genetic mechanisms having been presented in the last few years, there are now new ideas on drugs that could be tested in clinical trials. As mentioned above, some of these trials are already underway. Others are in the planning stages, and still others are only being contemplated. It would be best to have a priority of agents to be tested based on the most likely to be successful. Fortunately, the National Institute of Neurological Diseases and Stroke (NINDS) has already established an Oversight Committee to guide the Institute in this type of strategy.

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